REMARKS

Claims 1-11 are pending in the present application. A Rule 132 Declaration of Dr. Chaitanya R. Divgi, a coauthor of the publication, Loh et al., The Journal of Nuclear Medicine, 39: 484-489 (1998) is attached hereto. Additionally, a copy of the priority document U.S. Appl. Ser. No. 60/266,853, is attached hereto. No new matter is introduced.

August 22, 2007 Non-Final Office Action

According to the August 22, 2007 Non-Final Office Action, the finality of the previous Office Action has been withdrawn.

In response, Applicants acknowledge and appreciate the withdrawal of the final rejection.

In the Non-Final Office Action, however, the Examiner has maintained the obviousness rejections of claims 1-11 under 35 U.S.C. § 103(a) as being unpatentable over Oosterwijk et al. (a) (WO 88/08854, Published 11/17/1988) in view of Oosterwijk et al. (b) (Seminars in Oncology. 1995. 22(1):34-41), in view of Robinson et al. (U.S. Patent No. 5,618,920; issued 4/8/1997) and in view of Queen et al. (U.S. Patent No. 5,530,101; issued 6/25/1996). Additionally, the Examiner maintained the obviousness rejection of claims 1-11 under 35 U.S.C. § 103(a) as being obvious over Weijtens et al. (The Journal of Immunology, 157:836-843, 1996) in view of Oosterwijk et al. (b) (Seminars in Oncology. 1995. 22(1):34-41), in view of Orlandi et al (Proc. Natl. Acad. Sci. USA, 86:3833-3837, 1989), in view of Cabilly et al. (U.S. Patent No. 4,816,567; issued 3/28/1989) in view of Robinson et al. (U.S. Patent No. 5,618,920; issued 4/8/1997), in view of Huston et al. (U.S. Patent No. 5,258,498, issued 11/93) and in view of Queen et al. (U.S. Patent No. 5,530,101; issued 6/25/1996).

As grounds for maintaining these rejections, the Examiner contends that the submitted Declarations of Dr. Reinder LH Bolhuis, Egbert Oosterwijk and Sven Warnaar "do not address the agreements under which the G250 antibody and hybridoma were

provided, whether any restrictions were made and whether or not the G250 antibody and hybridoma were provided under a secrecy or confidentiality agreement."

In response, the Applicants assert that each of the submitted Declarations completely address each of the Examiner's alleged deficiencies. For example, paragraphs 2-3 of Dr. Bolhuis' Declaration attests that, inter alia, "the hybridoma cell was not released to anyone other than the team members who were under [his] control and supervision. . . [and] the hybridoma cell . . . was received from Prof. Sven Warnaar under confidentiality agreements that strictly restricted the use, disclosure and distribution thereof to the approval by Prof. Warnaar." (amended and emphasis added). Moreover, Oosterwijk states in paragraph 3 of his Declaration that "the hybridoma cell . . . was provided . . . under a confidentiality agreement that strictly restricted the use, disclosure and distribution thereof to the approval by [himself] and Dr. Warnaar . . . ." (amended and emphasis added). Finally, another example of the restrictions required by the inventors is provided by Warnaar's Declaration in paragraph 3. Warnaar declared that the confidentiality agreements under which the hybridoma cell was provided by him "bound the authors of the Weijtens reference to an obligation not to distribute the hybridoma cell to third parties without [Warnaar's] written approval." (amended and emphasis added). The Applicants respectfully submit, therefore, that the submitted Declarations lack the deficiencies described by the Examiner and that the rejections made under 35 U.S.C. § 103(a) on these grounds should be withdrawn.

The Examiner's remaining grounds for maintaining the 35 U.S.C. § 103(a) rejections rely on two references, each of which, the Examiner contends, demonstrates that the G250 hybridoma cells were publicly available. In the first of the two references, the Examiner cited Loh et al., The Journal of Nuclear Medicine, 39: 484-489 (1998) for its teachings of the G250 antibody.

In response, Applicants are submitting herewith a Rule 132 Declaration by Dr. Chaitanya R. Divgi, a co-author of Loh et al., The Journal of Nuclear Medicine, 39: 484-489 (1998). The Declaration states that the G250 antibody described in Loh et al. was provided by the inventors under confidentiality agreement that restricted its use and

distribution to third parties. The Applicants respectfully submit, therefore, that the Loh et al. reference does not provide evidence that either the G250 antibody or the G250 hybridoma was publicly available.

The remaining reference which the Examiner cites for maintaining the 35 U.S.C. § 103(a) rejections is Ritter et al. (published U.S. Pat. Appl. No. 2003/0040027). According to the Examiner, Ritter et al. demonstrates that G250 was on sale and, like Loh et al., provides evidence that G250 antibody was publicly available at the time of filing of the present application.

In response, Applicants wish to draw the Examiner's attention to the date of priority for Ritter et al. This published patent application is based on a priority date of August 16, 2001. On the other hand, the present application claims priority to U.S. Appl. Ser. No. 60/266,853, which was filed on February 7, 2001 and antedates Ritter et al. by more than six months. In Figure 1 of U.S. Appl. Ser. No. 60/266,853, the sequences of the VH domain and the VL domain of the G250 antibody are indicated at the time of filing. The subject matter of the present claims is thus supported by the first priority of February 7, 2001. Consequently, the Applicants assert that the Ritter et al. published patent application is not prior art upon which the Examiner can rely. Simply put, one of ordinary skill in the art could not use the hybridoma producing the monoclonal G250 if they could not have access to it. Applicants, therefore, respectfully request reconsideration and withdrawal of the obviousness rejections under 35 U.S.C. § 103(a).

In view of the foregoing, it is submitted that the present application is now in condition for allowance. Reconsideration and allowance of the Application is requested. The Director is authorized to charge any fees or overpayment to Deposit Account No. 02-2135.

Respectfully submitted,

By _____

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Attachment: Rule 132 Declaration of Chaitanya R. Divgi
Priority document U.S. Appl. Ser. No. 60/266,853

#1452799

PCT/EP 02/01283

REC'D 24 APR 2002
WIPO PCT

PA 525489

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

P1

February 20, 2002

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: *60/266,853*
FILING DATE: *February 07, 2001*

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1 (a) OR (b)

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

M. K. HAWKINS
Certifying Officer

PROVISIONAL PATENT APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION for patent under 37 C.F.R. §1.53(c).

Docket Number	100564-00047	Type a plus sign (+) inside this box	+

INVENTOR(S)/APPLICANT(S)			
LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
BOLHUIS	Reinier	L.H.	2451 XC Leimulden, NL

TITLE OF THE INVENTION (280 characters max)

METHOD OF PRODUCING RECOMBINANT ANTIBODIES

CORRESPONDENCE ADDRESS

Arent Fox Kintner Plotkin & Kahn PLLC
1050 Connecticut Avenue, N.W., Suite 600
Washington, D.C. 20036

STATE	Washington, D.C.	ZIP CODE	20005-5701	COUNTRY	U.S.A.

ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification	*Number of Pages*	10	☐	Small Entity Statement
☒ Drawing(s)	*Number of Sheets*	2	☐	Other (specify)

METHOD OF PAYMENT *(check one)*

☐ A check or money order is enclosed to cover the Provisional filing fees ☒ The Commissioner is hereby authorized to charge our Deposit Account No. 01-2300 in the amount of $150.	PROVISIONAL FILING FEE AMOUNT(S)	$150.00

The invention was made by an agency of the United States Government or under a contact with an agency of the United States Government.

☒ No
☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

SIGNATURE _____ Date: February 7, 2001

TYPED or PRINTED NAME Charles M. Marmelstein REGISTRATION NO. 25,895

☐ Additional inventors are being named on separately numbered sheets attached hereto.

PROVISIONAL APPLICATION FILING ONLY

Method of producing recombinant antibodies

Description

The invention relates to novel nucleic acid sequences which encode an antibody suitable in the field of tumor diagnostics and therapeutics. Further, a method of producing recombinant antibodies is provided, wherein the novel nucleic acid sequences are employed.

The monoclonal antibody G250, subclass IgG1, recognizes an antigen preferentially expressed on membranes of renal cell carcinoma cells (RCC) and not expressed in normal proximal tubular epithelium. The antibody G250 was obtained by immunizing a mouse with cell homogenates from primary RCC lesions obtained from different patients (Oosterwijk et al., Int. J. Cancer 38 (1986), 489-494).

The antibody G250 as well as chimeric derivatives has been used in clinical studies (Steffens et al., J. Clin. Oncol. 15 (1997), 1529-1537). The nucleic acid sequence coding for the antigen-binding site of G250, however, has not been published yet.

Thus, a subject matter of the present invention is a nucleic acid encoding the antigen-binding site of the heavy chain of an antibody comprising a nucleotide sequence encoding the CDR3 region as shown in Fig. 1 (designated H3).

The nucleic acid sequence furthermore preferably comprises a nucleotide sequence encoding the CDR2 region as shown in Fig. 1 (designated H2) and/or a nucleotide sequence encoding the CDR1 region as shown in Fig. 1 (designated H1). More preferably, the nucleotide sequences encoding the CDR3, CDR2 and CDR1 regions are arranged in a manner wherein a

polypeptide encoded by the nucleotide sequence is capable of forming an antigen-binding site having substantially the same characteristics as the heavy chain antigen-binding site of the monoclonal antibody G250.

A further aspect of the present invention relates to a nucleic acid encoding the antigen binding site of the light chain of an antibody comprising a nucleotide sequence encoding the CDR3 region as shown in Fig. 1 (designated L3).

Preferably the nucleic acid further comprises a nucleotide sequence encoding the CDR2 region as shown in Fig. 1 (designated L2) and/or a nucleotide sequence encoding the CDR1 region as shown Fig. 1 (designated L1).

More preferably, the nucleic acids encoding the CDR3, CDR2 and CDR1 region are arranged such that a polypeptide encoded by the nucleic acid has substantially the same antigen-binding characteristics as the light chain antigen binding site of the antibody G250.

In the nucleic acid of the invention the complement determining regions CDR3, CDR2 and CDR1 are preferably separated by nucleotide sequence portions encoding so-called framework regions of antibodies. The framework regions may be derived from any species, e.g. from mouse (as shown in Fig. 1). It is, however, possible to use framework regions from different species, e.g. human framework regions. It should be noted that also the CDR1, CDR2 and/or CDR3 regions may be modified, e.g. by modifying the nucleotide sequence resulting in a modified nucleotide sequence encoding a polypeptide sequence differing from the polypeptide sequence as depicted in Fig. 1, provided that the antigen-binding specificity remains substantially the same. More preferably, however, the nucleic acid sequences of the heavy chain and light chain CDR3 sequence

and of the CDR2 and CDR1 sequence, if present, have the nucleotide sequence as depicted in Fig. 1.

The nucleic acid sequences of the present invention may be located on a recombinant vector comprising at least a copy of a heavy chain nucleic acid and/or at least a copy of a light chain nucleic acid. The heavy chain nucleic acid and the light chain nucleic acid are preferably in operative linkage with an appropriate expression control sequence, particularly an expression control sequence which is functionally in eukaryotic cells. The heavy chain and the light chain nucleic acid may be located on the same vector in operative linkage with a single expression control sequence or with separate expression control sequences which may be the same or different. Alternatively, the heavy chain nucleic acid sequence and the light chain nucleic acid sequence may be located on different recombinant vectors, each in operative linkage with a separate expression control sequence.

Further, the present invention comprises a method for the recombinant production of a polypeptide having an antigen-binding site comprising:

(a) providing a nucleic acid as defined above,
(b) introducing the nucleic acid into a suitable host cell,
(c) culturing the host cell under suitable conditions in a medium whereby an expression of the nucleic acid takes place and
(d) obtaining the expressed product from the medium and/or the host cell.

Preferably, the host cell is a eukaryotic cell, particularly a mammalian cell. For example, the host cell may be a non-producer hybridoma cell or a CHO cell.

Between steps (a) and (b) of the method as outlined above a modification of the nucleic acid sequence may take place, wherein the modification

substantially does not alter the amino acid sequence of the antigen-binding site of the polypeptide to be expressed. The expressed product obtained by the method as outlined above may be used for the preparation of a diagnostic or therapeutic agent. Thereby it is possible to couple the antigen-binding polypeptide to a diagnostic marker, e.g. a marker which is useful for in vitro diagnostic methods using a sample obtained from a patient, e.g. a body fluid or a tissue section, or for quality control. Further, the expressed product may be coupled to a diagnostic marker which is suitable for in vivo applications, e.g. a radioactive marker which is suitable for radioimaging procedures. For therapeutical applications the expressed product may be coupled to a cytotoxic agent, e.g. a radionuclide, a toxin such as cholera toxin or ricin.

The expressed product which is obtained by the method as outlined above is a polypeptide having an antigen-binding site. For example, the expressed product may be selected from antibodies, e.g. chimerized antibodies, humanized antibodies, heterobispecific antibodies, single chain antibodies etc. and from antibody fragments, e.g. antibody fragments containing an antigen-binding site wherein said antibody fragments may be obtained by proteolytic digestion of whole antibodies or by recombinant techniques.

For example, single chain antibodies or antibody fragments may be prepared as described in Hoogenboom et al. (Immunol. Rev. 130 (1992), 41-68), Barbas III (Methods: Companion Methods Enzymol. 2 (1991), 119) and Plückthun (Immunochemistry (1994), Marcel Dekker Inc. Chapter 9, 210-235).

Further, the present invention is explained in detail by the following example:

Example 1

Isolation, cloning and sequencing of the G250 tumor-associated antigen-specific immunoglobulin variable heavy and light chain domains from the G250 monoclonal antibody producing hybridoma.

General strategy

The variable region genes for the heavy and light chains, which determine the binding specifity of the antibody, were cloned from the G250 murine hybridoma using standard cloning techniques as described in Molecular Cloning; A Laboratory Manual (Cold Spring Harbour Press, Cold Spring Harbour, N.Y.) by Maniatis, T. et al.

The strategy for cloning the variable regions for the heavy and light chain genes from the G250 hybridoma was achieved by PCR amplification of cDNA obtained from the G250 monoclonal antibody producing hybridoma cells.

Cloning of G250 VH and VL cDNA

Obtaining the G250 VH and VL chain sequences from the G250 monoclonal antibody producing hybridoma was achieved by PCR (Maniatis, T. et al.) amplification of cDNA obtained from the respective clone.

To obtain cDNA, total RNA was isolated from the G250 producing hybridoma cells according to the method by Chomczynski et al. (Chomczynski, P. and Sacchi, N., Anal. Biochem. 162 (1987), 156-159) and converted into cDNA essentially as described by Maniatis et al. Amplification of cDNA sequences by PCR is possible only, if the sequence of the gene of interest is known. In general, for PCR two primers complementary to the 5'-end and the 3'-end of the sequence are used as

the initiation point of DNA synthesis. Because the sequence of the 5'-ends of the VH and VL chain from the G250 monoclonal antibody producing hybridoma cells were unknown, the PCR method, referred to as RACE (rapid amplification of cDNA ends) was used to amplify the VH and VL chain. This was achieved by employing anchor and anchor-poly-C primers and the constant VH and VL-primers as shown in Fig 2. The VH and VL fragments were purified and ligated into pGEM11 as described by Maniatis et al. A ligation mixture was introduced into bacteria, which were selected and expanded. DNA was isolated from the selected bacterial colonies and analyzed by restriction enzyme digestion to confirm the presence of the amplified VH and VL fragments. Three positive colonies were subjected to DNA sequencing. The sequences of these three individual clones were compared and found to be identical.

Portions of the resulting sequences including the antigen-specific CDR regions are shown in Fig. 1.

Claims

1. Nucleic acid encoding the antigen-binding site of the heavy chain of an antibody comprising a nucleotide sequence encoding the CDR3 region as shown in Fig. 1 (designated H3).

2. The nucleic acid of claim 1 further comprising a nucleotide sequence encoding the CDR2 region as shown in Fig. 1 (designated H2).

3. The nucleic acid of claim 1 or 2 comprising a nucleotide sequence encoding the CDR1 region as shown in Fig. 1 (designated H1).

4. The nucleic acid of any one of claims 1-3 wherein the nucleotide acid sequence is as depicted in Fig. 1.

5. Nucleic acid encoding the antigen-binding site of the light chain of an antibody comprising a nucleotide sequence encoding the CDR3 region as shown in Fig. 1 (designated L3).

6. The nucleic acid of claim 5 further comprising a nucleotide sequence encoding the CDR2 region as shown in Fig. 1 (designated L2).

7. The nucleic acid of claim 5 or 6 further comprising a nucleotide sequence encoding the CDR1 region as shown in Fig. 1 (designated L1).

8. The nucleic acid of any one of claims 5-7 wherein the nucleotide acid sequence is as depicted in Fig. 1.

9. Nucleic acid encoding the antigen-binding site of antibody comprising at least one of nucleic acid of any one of claims 1-4 and at least one of nucleic acid of any one of claims 5-8.

10. Recombinant vector comprising at least a copy of a nucleic acid of any one of claims 1-4 and/or at least a copy of a nucleic acid of any one of claims 5-8.

11. Method for the recombinant production of a polypeptide having an antigen-binding site comprising:

(a) providing the nucleic acid as defined in any one of claims 1-9,

(b) introducing the nucleic acid into a suitable host cell,

(c) culturing the host cell under suitable conditions in a medium whereby an expression of the nucleic acid takes place, and

(d) obtaining the expressed product from the medium and/or the host cell.

12. The method of claim 11 wherein the host cell is a mammalian cell.

13. The method of claims 11 or 12 wherein between steps (a) and (b) a modification of the nucleic acid takes place wherein the modification substantially does not alter the amino acid sequence of the antigen-binding site of the polypeptide to be expressed.

14. The method of any one of claims 11-13 further comprising preparing a diagnostic or therapeutic agent from the expressed product.

15. The method of claim 14 wherein the expressed product is coupled to a diagnostic marker.

16. The method of claim 14 wherein the expressed product is coupled to a cytotoxic agent.

17. The method of claims 11-16 wherein the expressed product is selected from antibodies and antibody fragments.

Abstract

The invention relates to novel nucleic acid sequences which encode an antibody suitable in the field of tumor diagnostics and therapeutics. Further, a method of producing recombinant antibodies is provided, wherein the novel nucleic acid sequences are employed.

cl 07.02.2001

Figure 1

VH G250

```
1/1                                     31/11                                   61/21                                   91/31
gac gtg aag ctc gtg gag tct ggg gga ggc tta gtg aag ctt gga ggg tcc ctg aaa ctc tcc tgt gca gcc tct gga ttc act ttc agt aac tat tac atg tct tgg gtt cgc cag act
D   V   K   L   V   E   S   G   G   G   L   V   K   L   G   G   S   L   K   L   S   C   A   A   S   G   F   T   F   S   N   Y   Y   M   S   W   V   R   Q   T
                                                                                                                        ___________________
                                                                                                                                H1

121/41                                  151/51                                  181/61                                  211/71
cca gag aag agg ctg gag ttg gtc gca gcc att aat agt gat ggt ggt atc acc tac tat cta gac act gtg aag ggc cga ttc acc att tcc aga gac aat gcc aag aac acc ctg tac
P   E   K   R   L   E   L   V   A   A   I   N   S   D   G   G   I   T   Y   Y   L   D   T   V   K   G   R   F   T   I   S   R   D   N   A   K   N   T   L   Y
                                    _________________________________________________________________
                                                                    H2

241/81                                  271/91                                  301/101                                 331/111
ctg caa atg agc agt ctg aag tct gag gac aca gcc ttg ttt tac tgt gca aga cac cgc tcg ggc tac ttt tct atg gac tac tgg ggt caa gga acc tca gtc acc gtc tcc tca
L   Q   M   S   S   L   K   S   E   D   T   A   L   F   Y   C   A   R   H   R   S   G   Y   F   S   M   D   Y   W   G   Q   G   T   S   V   T   V   S   S
                                                                        _______________________________________
                                                                                        H3
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VL G250

```
1/1                                     31/11                                   61/21                                   91/31
gac att gtg atg acc cag tct caa aga ttc atg tcc aca tca gta gga gac agg gtc agc atc acc tgc aag gcc agt cag aat gtg gtt tct gct gtt gcc tgg tat caa cag aaa cca
D   I   V   M   T   Q   S   Q   R   F   M   S   T   S   V   G   D   R   V   S   I   T   C   K   A   S   Q   N   V   V   S   A   V   A   W   Y   Q   Q   K   P
                                                                                            _____________________________________________
                                                                                                                L1

121/41                                  151/51                                  181/61                                  211/71
gga caa tct cct aaa cta ctg att tac tcg gca tcc aat cgg tac act gga gtc cct gat cgc ttc aca ggc agt gga tct ggg aca gat ttc act ctc acc att agc aat atg cag tct
G   Q   S   P   K   L   L   I   Y   S   A   S   N   R   Y   T   G   V   P   D   R   F   T   G   S   G   S   G   T   D   F   T   L   T   I   S   N   M   Q   S
                                    ___________________________
                                                L2

241/81                                  271/91                                  301/101
gaa gac ctg gct gat ttt ttc tgt caa caa tat agc aac tat ccg tgg acg ttc ggt gga ggc acc aag ctg gaa atc aaa
E   D   L   A   D   F   F   C   Q   Q   Y   S   N   Y   P   W   T   F   G   G   G   T   K   L   E   I   K
                                ___________________________________
                                                L3
```

CDRs; H1, H2, H3 & L1, L2, L3
CDR definition according to Kabat scheme

Figure 2

Primers used for PCR amplification of G250 VH and VL regions

Anchor and anchor poly C primers:

Anchor: 5'-GCA TGC GCG CGG CCG CGG AGG CC-3'

Anchor poly C: 5'-GCA TGC GCG CGG CCG CGG AGG $CC(C)_{12}$-3'

Constant primers:

VH-primers: 5'-CTC TAA GCT TGG CTC AAA CAC AGC
GAC CTC GGA TAC AGT TGG TGC AGC-3'

VL-primers: 5'-CTC TTC TAG AGA GTC TCT CAG CTG
GTA GGA TAC AGT TGG TGC AGC-3'

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	10/635,908
Applicant	:	Reinier LH Bolhuis *et al.*
Filed	:	August 7, 2003
TC/A.U.	:	1643
Examiner	:	Parithosh K. Tungaturthi
Docket No.	:	2923-552
Customer No.	:	6449
Confirmation No.	:	7844

DECLARATION

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Sir:

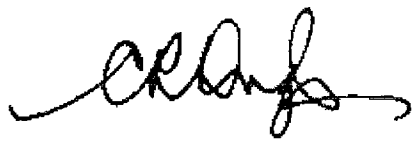
I, Chaitanya R. Divgi, declare as follows.

1. I am a coauthor of a publication, Loh et al., The Journal of Nuclear Medicine, 39: 484-489 (1998).

2. G250 monoclonal antibody was mentioned in the publication. The monoclonal antibody used and described in the publication was received from the inventors under confidentiality agreement that restricted the use and distribution thereof. We were to not make the monoclonal antibody available to any third party and, to the best of my knowledge, did not do so. This monoclonal antibody was provided to the research team of co-authors from the Ludwig Institute for Cancer Research and Memorial Sloan-Kettering Cancer Center under restrictions as to further distribution.

3. I state that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further

that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.



Dr. Chaitanya R. Divgi

October 22, 2007
Date

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